UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: December 8, 2016

SUBJECT: **Benzovindiflupyr:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of September 1, 2016: Recommendation on the Need for a Comparative Thyroid Assay Waiver Request.

PC Code: 122305
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
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MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
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40 CFR: N/A

FROM: Sarah Dobreniecki, Ph.D.
Executive Secretary, HASPOC
Health Effects Division (7509P)

THROUGH: Anwar Dunbar, Ph.D., Co-Chair
Jeff Dawson, Co-Chair
HASPOC
Health Effects Division (7509P)

TO: Ronnie J. Bever Jr., Ph.D., DABT, Toxicologist, Risk Assessor
Michael Metzger, Branch Chief
Risk Assessment Branch VI (RAB VI)
Health Effects Division (7509P)

MEETING ATTENDEES:

HASPOC Members: Jonathan Chen, Ray Kent, John Kough, Anna Lowit, Elizabeth Mendez, Michael Metzger, Jonathan Leshin, Jeffrey Dawson, Anwar Dunbar, Sarah Dobreniecki

Presenter: Ronnie J. Bever Jr.

Other Attendees: Sarah Gallagher, Hannah Pope-Varsalona

I. PURPOSE OF MEETING

Risk Assessment Branch V/VII is currently preparing a new use human health risk assessment for benzovindiflupyr. The toxicology database for benzovindiflupyr demonstrates thyroid tumors in male rats and thyroid focal c-cell hyperplasia in female rats from the combined chronic toxicity/carcinogenicity study at the LOAEL (27/30 [M/F] mg/kg/day), but the submitted toxicity studies do not include a comparative thyroid assay. The Hazard and Science Policy Council (HASPOC) met on September 1, 2016 to discuss the need for a comparative thyroid assay.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

Syngenta has requested U.S. registration of the new active ingredient fungicide benzovindiflupyr for use on cereals (wheat, triticale, barley, rye and oat), corn, cotton, cucurbits, fruiting vegetables, small fruit vines climbing (except fuzzy kiwifruit), legumes, peanuts, pome fruit, canola, tuberous and corm vegetables, lowbush blueberries (non-bearing), turf and ornamentals. Syngenta has also requested that tolerances for benzovindiflupyr on imported coffee and sugarcane be established. The current new use action is for bulb onions (Subgroup 3-07A) and green onions (Subgroup 3-07B).

The most recent risk assessment for benzovindiflupyr was conducted in 2015 (Drew, 2015, D408961, D408960). Endpoints for risk assessment have been selected for acute dietary exposure (all populations) based on a NOAEL of 10 mg/kg/day from an acute neurotoxicity study (100X uncertainty factor). The endpoint for chronic dietary, short-term incidental oral, and short- and intermediate-term inhalation is taken from the 2-generation reproduction study and includes decreased body weight and decreased food consumption in parental animals, and in the offspring includes increases in liver weights, centrilobular hepatocellular hypertrophy, increased incidence of cell hypertrophy in the pars distalis of the pituitary, reduced body weight, delayed preputial separation, and decreased spleen weights. A POD and endpoint of concern was not identified and quantification of dermal risk is not required, since no systemic or dermal toxicity was seen following repeated dermal applications of benzovindiflupyr at the Limit Dose (1000 mg/kg/day) to rats for 28 days. Additionally, there are no concerns for developmental, reproductive, neurotoxicity, or immunotoxicity. The cancer classification is "Suggestive Evidence of Carcinogenic Potential" and as such quantification of carcinogenicity is not required. The RfD would be protective of non-carcinogenic and carcinogenic effects observed in the rat carcinogenicity study or mode of action studies conducted at higher doses.

The 2015 risk assessment addressed exposures and risk estimates associated with the dietary, occupational, and residential uses of benzovindiflupyr. At the 95th percentile, the risk estimate was 10% of the aPAD for the general U.S. population. The risk estimate for the most highly exposed subgroup, children 1-2 years old, was 30% of the aPAD. At the 95th percentile, the risk estimate was 4% of the cPAD for the general U.S. population. The risk estimate for the most highly exposed subgroup, children 1-2 years old, was 14% of the cPAD. Since no dermal hazard was identified for benzovindiflupyr in the toxicological database, only inhalation exposure assessments were conducted for residential handlers. Inhalation margins of exposure (MOEs) are well above the level of concern (LOC) of 100 for all scenarios assessed and are not of

concern (estimated ST inhalation MOEs are all ≥ 180,000). The short-term incidental oral exposure and risk estimates resulting from residential post-application exposures provide incidental oral MOEs for children ranging from 8,000 to 3,600,000 on the day of application, using default input values, and are not of concern. The short-term aggregate risk estimate for adults (MOE=2500) and children (MOE=680) are below HED's level of concern.

b. Toxicity Profile

Benzovindiflupyr is a pyrazole carboxamide fungicide proposed for foliar use on numerous crops and on turf grass and ornamentals. The pesticidal mode of action of this group of fungicides is inhibition of succinate dehydrogenase (SDH, mitochondrial Complex II). SDH is a functional part of the tricarboxylic acid cycle (TCA), the mitochondrial electron transport chain and oxidative phosphorylation utilized to synthesize ~90% of the energy in eukaryotes needed for protein synthesis, DNA synthesis, work, and ion pumping.

The rat is the most sensitive species tested and the target organs are the liver, thyroid and kidneys. Hepatotoxicity was manifested as changes in liver weights, liver hypertrophy, decreased triglycerides, and increased urea. The kidney effects were tubular cell pigment deposits and changes in the tubular basophilia. Distended large intestines, soft feces and hyperplasia of the colon and caecum occurred in the mouse studies. Indications of general malaise, including decreased body weight, body weight gain, food consumption, decreased activity, decreased grip strength, piloerection, decreased response to stimulus, hunched posture, gait changes and ataxia were reported in a number of studies. The pituitary pars distalis had hypertrophy, while the thyroid and mammary glands had hyperplasia. In several studies, females tended to be the more sensitive gender.

Benzovindiflupyr produced effects in rat fetuses in developmental toxicity studies at maternally toxic doses (i.e. decreased fetal weight and ossification). In the rabbit developmental study, there were no adverse effects in either the does or the fetuses at the highest dose tested. In rat reproduction studies, offspring effects occurred at higher doses higher than those causing parental effects, thus there was no quantitative increase in sensitivity in rat pups. There were no single-dose developmental effects identified in the developmental toxicity studies in rats or rabbits. No evidence of specific neurotoxicity were observed in the acute oral (gavage) and subchronic oral (dietary) neurotoxicity (ACN and SCN) studies in rats, conducted on the benzovindiflupyr technical product. Immune system toxicity was negative. Benzovindiflupyr did not display systemic effects in the 28-day dermal study, even at the limit dose of 1000 mg/kg/day.

The CARC, in accordance with the Agency's 2005 Guidelines for Carcinogen Risk Assessment, classified benzovindiflupyr as showing "*Suggestive Evidence of Carcinogenic Potential*" based on the presence of granular cell tumors of the brain in male rats. In addition, there is no concern for mutagenicity.

Benzovindiflupyr has low acute toxicity by the dermal and inhalation routes, with moderate toxicity via the oral route. It is not a dermal sensitizer, but causes mild skin irritation and moderate eye irritation.

III. STUDY WAIVER REQUEST

Comparative Thyroid Study

A number of pesticides have been shown to perturb thyroid hormone homeostasis via reduction of circulating thyroid hormones[1]. This perturbation may be the initial, critical effect leading to adverse effects on the developing nervous system[2,3]. When a chemical causes thyroid effects, there is inherent uncertainty about potential impacts to the developing brain in response to changing thyroid levels. There is also a lack of empirical data on whether pregnant women or the fetus are more or less susceptible, compared to adults, to the impact of chemicals that alter thyroid hormone homeostasis. This gap makes predictions on developmental susceptibility based on data from adult organisms difficult and very uncertain. The current 40 CFR Part 158 Toxicology Data Requirements do not include thyroid hormone measurements during these potentially sensitive lifestages. The EPA has developed guidance for conducting a comparative thyroid assay[4] that uses a mechanistic approach to generate thyroid-specific data which can address the uncertainties associated with lifestage susceptibility and allow for the establishment of PODs that would be protective of potential effects of thyroid function disruption in pregnant females on the fetus and newborn.

In a chronic toxicity and carcinogenicity study (MRID 48604446) at the LOAEL (30/27 mg/kg/day in M/F; highest dose tested), focal c-cell hyperplasia of the thyroid was observed in females, and thyroid follicular cell adenomas were observed in males. However, the CARC concluded that a non-genotoxic mode of action for thyroid tumors observed in male rats has been established as a result of upregulation of UDPGT, increased clearance of T3 and T4 hormones and increased TSH levels, resulting in increased thyroid cell proliferation, which progress to form thyroid tumors. Thus, without up-regulation of metabolic enzymes in the liver, thyroid function disruption is not expected in the adults (including the pregnant females). An effect on the fetus would also not be expected as the developing fetus is largely dependent on the mother's supply of thyroid hormone[5].

Risk Implications

Based on the calculation of aggregate exposures using the average residues for existing crops, and incorporating proposed onion and sugarcane tolerances from the registrant, the team determined that short-term aggregate risks are low for both adults and children (MOEs $\geq$ 2300). For residential handler inhalation exposure assessments, margins of exposure (MOEs) are well above the level of concern (LOC) of 100 for all scenarios assessed and are not of concern

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[1] Hurley et al. 1998. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ. Health Perspect. 106(8): 437-445.
[2] Chan S and Kilby MD. 2000 Thyroid hormone and central nervous system development. J Endocrinol 165:1-8
[3] Fisher DA. 2000. The importance of early management in optimizing IQ in infants with congenital hypothyroidism. J Pediat 136:274-274.
[4] US EPA 2005. Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals. Washington, DC.
[5] Morreale de Escobar, G, Obregón, MJ, Escobar del Rey, F. 2004. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Practices & Research Clinical Endocrinology & Metabolism, Volume 18, Issue 2: 225-248.

(estimated ST inhalation MOEs are all ≥ 180,000). The short-term incidental oral exposure and risk estimates resulting from residential post-application exposures provide incidental oral MOEs for children ranging from 8,000 to 3,600,000 on the day of application, using default input values, and are not of concern.

VI. HASPOC CONCLUSIONS

Based on a WOE approach, considering all the available hazard and exposure data for benzovindiflupyr, the HASPOC concludes that the comparative thyroid assay for benzovindiflupyr is not required at this time. This approach considered the identified mode of action for thyroid perturbation. In addition, the current points of departere (PODs) selected for risk assessment are adequately protective of potential thyroid effects in the young. Using the current PODs, risk estimates are low for the current uses and provide an adequate margin of safety to protect for any potential lifestage susceptibilities.